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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/061,019	04/15/1998	KATHERINE H. KODAMA	GC272D2	1225

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GENENCOR INTERNATIONAL, INC.  
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EXAMINER

RAO, MANJUNATH N

ART UNIT PAPER NUMBER

1652

DATE MAILED: 06/26/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Applicati n No.

09/061,019

Applicant(s)

KODAMA ET AL.

Examiner

Manjunath N. Rao, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 11-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### **DETAILED ACTION**

Claims 11-18 are still at issue and are present for examination.

Applicants' amendments and arguments filed on 4-18-03 and 4-24-03, paper No.12 and 14, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

#### ***Sequence submission***

Applicant's submission of sequence information in paper No.14 has been entered into the USPTO sequence database.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 and claims 12-18 which depend from claim 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 recites the phrase "amino acid sequence comprising a desired glycosyltransferase from which the transmembrane anchor coding region has been deleted." in several instances. It is well known in the art that amino acids sequences do not encode a peptide or a polypeptide. Amending the claim by deleting the incorrect phrase would overcome this rejection.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a fusion protein comprising a signal peptide from glucoamylase,  $\alpha$ -amylase and aspartyl protease, a secreted polypeptide such as glucoamylase from *A. niger* var. *awamori* and an optional cleavable linker followed by a desired glycosyltransferase lacking a transmembrane anchor region, does not reasonably provide enablement for such a fusion protein comprising any signal peptide and any secreted polypeptide fused with an optional cleavable linker followed by a desired glycosyltransferase lacking a transmembrane anchor region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 11-12 are so broad as to encompass a fusion protein comprising any signal peptide from any source and any secreted polypeptide secreted from *Aspergillus*. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of signal peptides and secreted polypeptide sequences broadly

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encompassed by the claims. Claims are drawn to fusion proteins comprising any signal peptide functional in *Aspergillus* and secreted polypeptide, secreted normally from *Aspergillus*.

Applicants have neither not taught all the signal peptides functional in *Aspergillus* nor all the secreted polypeptides secreted from *Aspergillus*. Applicants have also not shown that any or all signal peptides that may become available to those skilled in the art can be functional in *Aspergillus*. On same lines applicants have also not provided all polypeptides secreted from *Aspergillus*. Since the invention requires signal peptide sequence to be functional in *Aspergillus* and secreted polypeptides need to be secreted from *Aspergillus*, those skilled in the art require a knowledge of and guidance with regard to which specific signal peptides and which specific secreted polypeptides can be used and a detailed knowledge of how to obtain those sequences. However, in this case the disclosure is limited to the fusion proteins comprising signal peptide from glucoamylase,  $\alpha$ -amylase and aspartyl protease and a secreted polypeptide such as glucoamylase all of which are obtained from *A.niger* var. *awamori*. It would require undue experimentation of the skilled artisan to make the fusion protein comprising determination of all those signal peptide sequences that are able to function in all or any species of *Aspergillus* and also to select those secreted polypeptide normally secreted from any species of *Aspergillus* and make and use fusion proteins using such polypeptides. The specification is limited to teaching the use of a fusion protein comprising the signal peptide selected from glucoamylase,  $\alpha$ -amylase and aspartyl protease and comprising the glucoamylase as secreted protein of *A.niger* var. *awamori*. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein

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Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and that modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass fusion proteins comprising any signal peptide or any secreted polypeptide because the specification does not establish: (A) a rational and predictable scheme for identifying those signal peptides that are functional in any or all species of *Aspergillus*; (B) a rational and predictable scheme for identifying those secreted polypeptides that are secreted normally in any or all species of *Aspergillus*; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any signal peptide and secreted polypeptide in the fusion protein. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance,

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determination of fusion proteins having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11-13 are directed to fusion polypeptides comprising signal peptides and secreted polypeptides. Claims 11-13 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides that have not been disclosed in the specification. No description has been provided of the signal peptides and secreted polypeptide sequences encompassed by the claim. No information, beyond the characterization of the function that they are functional in *Aspergillus* has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e., signal peptide of glucoamylase of *A.niger* var. *awamori* which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude

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that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawlis (a) et al. (US 5,679,543, issued 10-21-1997, filed 10-5-1994) or Lawlis (b) et al. (US 6,130,063, issued 10-10-2000, filed 10-5-1994) and Kitagawa et al. (BBRC, 1993, Vol. 194(1):375-382.).

Claims 11-18 are drawn to a fusion polypeptide wherein the polypeptide comprises from the N-terminal side a signal peptide functional in *Aspergillus*, a secreted polypeptide or a portion thereof secreted from *Aspergillus* sp., an optional cleavable linker sequence followed by a glycosyltransferase having a deletion of the transmembrane anchor domain, wherein the glycosyltransferase is selected from sialyltransferase, galactosyltransferase or fucosyltransferase and wherein the signal peptide sequence is selected from the signal peptides of glucoamylase,  $\alpha$ -amylase etc., wherein the secreted polypeptide comprises either full length or portion of glucoamylase from *Aspergillus niger* var. *awamori*.



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Lawlis(a) et al. or Lawlis (b) et al. teach a fusion protein comprising a signal peptide and a secreted polypeptide or portion thereof from *Aspergillus sp.* such as *A.niger* and *A.awamori*, further comprising a cleavable linker region and any desired polypeptide sequence which when expressed in a fungal host cell such as *A.niger* and *A.awamori*, is expressed at an increased level when compared to a fungal cell expressing such a heterologous polypeptide that is not fused to a secreted *Aspergillus* polypeptide. The reference teaches that the increase in expression is significant such that it can be used for large scale production of heterologous proteins. However, the reference does not teach a fusion polypeptide comprising a glycosyltransferase in which the membrane anchor domain has been deleted as a heterologous polypeptide.

Kitagawa et al. teach the cloning and expression of a human sialyltransferase lacking the first 60 amino acids comprising the membrane anchor region in order to express said enzyme in a soluble form. In fact the reference teaches the expression of the enzyme as fusion protein comprising the human insulin signal sequence in the place of the signal peptide in the instant invention and comprising protein A in place of the secreted *Aspergillus* polypeptide in the instant invention. The reference teaches that such expression provides the sialyltransferase as a soluble protein which can be used for *in vitro* sialylation experiments.

With the above two references in hand, it would have been obvious to one of ordinary skill in the art to make a fusion protein as taught by Lawlis et al. using the sialyltransferase polypeptide lacking the membrane anchor domain taught by Kitagawa et al. in place of the fourth polypeptide sequence or the desired polypeptide position in the Lawlis et al. invention. It would also be within the knowledge of those skilled in the art to delete the membrane anchor domain

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from the sialyltransferase because retaining such a sequence would clearly hamper the secretion of the heterologous polypeptide because of the anchoring domain. Furthermore, judging from a literature survey it appears that such knowledge (i.e., deletion of the transmembrane anchor domain from glycosyltransferases to produce soluble form of the enzyme) was common in the art. One of ordinary skill in the art would have been motivated to do so as sialyltransferases have been known in the art to play an important role in glycosylation of recombinant polypeptides and are used for *in vitro* glycosylation purposes with more demand for pure enzyme and Lawlis et al. teach that expressing heterologous polypeptides as fusion polypeptides according to their teachings increases the yield of the heterologous polypeptide. One of ordinary skill in the art would have a reasonable expectation of success because Lawlis et al. provide methods for making such a polypeptide in general and Kitagawa et al. provide a glycosyltransferase lacking the transmembrane anchor domain.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that Lawlis et al. fail to describe a fusion polypeptide that is encompassed by the presently amended claims and that it fails to teach that a normally membrane bound enzyme such as a glycosyltransferase can be secreted. Examiner respectfully disagrees with the applicant that Lawlis et al. reference must teach such a limitation (normally membrane bound). This is because, instant claims do not have such a limitation. Lawlis et al. teach that any desired polypeptide can be used in their fusion polypeptide. Applicants also argue that Ward et al. is concerned with the improvement of a normally secreted enzyme and that nothing in Ward et al.

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teaches or suggests that a normally membrane-bound enzyme can be secreted if produced as a fusion protein. Examiner respectfully disagrees with such a conclusion by the applicant. Ward et al. clearly teach the use of signal sequence and the secreted polypeptide, glucoamylase, of *A. awamori* in a fusion protein for producing heterologous polypeptides in *Aspergillus* host cells for increasing yields. However, even irrespective of that, instant claims are not limited to only “normally membrane bound enzymes”. Applicants also argue that Kitagawa et al. fails to correct any deficiencies in Lawlis et al. or Ward et al. It is not clear to the Examiner as to what are those specific deficiencies. Examiner would like to remind applicants that the above rejection is an obviousness type rejection and that each of the reference need not teach each and every limitation of the claims and that it is the combination of the references that should meet the limitation of the claims. That said, Examiner reiterates the Kitagawa et al. specifically teach a glycosyltransferase lacking the membrane anchor region. The reference also teaches that by deleting such region the glycosyltransferase can be produced in a soluble form. While Kitagawa et al. do not teach whether the signal sequence they use is functional in *Aspergillus*, at the same time the reference does not specifically teach that the signal sequence is not functional in *Aspergillus*. Examiner has mainly used the reference to show the availability of a glycosyltransferase lacking membrane anchor domain and the reason/use for making such deletions.

Applicants also argue that attempts have been made previously in the art to produce glycosyltransferase as secreted proteins and that the yields were low and that the present inventive expression strategy involves removal of the transmembrane domain and fusion with *Aspergillus* secreted glucoamylase. Examiner respectfully disagrees. The instant expression

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strategy of using signal peptide sequence and secreted polypeptide sequence of glucoamylase from *Aspergillus* was well known in the art based on which Lawlis et al. made their vectors for expression of heterologous polypeptides. Similarly, the knowledge that removal of transmembrane domain from glycosyltransferase renders them expressible as soluble proteins was also well known in the art.

Therefore, contrary to applicants conclusion, the above invention would have been *prima facie* obvious to one of ordinary skill in the art and therefore the above rejection is maintained.

In view of the claim amendments, Examiner has withdrawn the rejection of claims 11-18 under 35 U.S.C. 103(a) as obvious over Ward et al. and Kitagawa et al.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-26 of U.S. Patent No. 5,679,543 or claims 17-26 of US 6,130,063 and in view of Kitagawa et al. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined

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application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 11-18 of the instant application are directed to fusion polypeptide comprising from the N-terminal a first, second, third and fourth sequence wherein the first sequence comprises signal peptide functional in *Aspergillus* and the second sequence comprises polypeptide secreted from *Aspergillus*, such as glucoamylase, followed by a third (optional) and fourth sequence comprising a cleavable linker polypeptide and a glycosyltransferase polypeptide without its membrane anchor domain. Claims 17-26 of both the reference patents while not totally identical to the instant claims are also directed to fusion polypeptide comprising from the N-terminal a first, second, third and fourth DNA sequence wherein the first and second sequences encode *Aspergillus* signal peptide and a polypeptide that can be secreted by *Aspergillus*, such as the glucoamylase followed by a third and fourth sequences comprising a cleavable linker polypeptide and the sequence of any desired polypeptide, which encompasses the polypeptide sequence of glycosyltransferase as claimed in the instant claims.

The inventions claimed in the instant application and in the reference patent are similar to one another. The portion of the specification (and the claims) in the reference patents, while broader than the claims in the instant application, includes several embodiments that would anticipate the invention claimed in the instant application. Claims of the instant application listed above cannot be considered patentably distinct over claims 17-26 of the reference patents

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when there is specifically recited embodiments that would either anticipate mainly claims 11-18 of the instant application or alternatively render them obvious. Alternatively, claims 11-18 cannot be considered patentably distinct over claims 17-26 of the reference patents when there is specifically disclosed embodiment in the instant application that falls within the scope of claims 17-26 of the reference patents because it would have been obvious to one having ordinary skill in the art to combine the teachings of the patent with that of Kitagawa et al. and slightly modify claims 17-26 of the reference patents by selecting a specifically disclosed embodiment that supports those claims i.e., a fusion protein sequence comprising all the subsequences of those taught in the reference patents except for the last sequence now limited to a glycosyltransferase lacking the transmembrane anchor domain. One of ordinary skill in the art would have been motivated to do this because the reference patents teach that the yields of heterologous polypeptides are higher when compared to other methods of expressing heterologous polypeptide and Kitagawa et al. reference teaches that recombinant sialyltransferase can be obtained in the soluble form when expressed without transmembrane anchor domain as a fusion protein.

In response to the previous Office action, applicants have traversed the above rejection by arguing that the patents fail to claim alone or in combination the present invention and the references fail to correct any deficiencies nor does it provide a basis of the instant rejection and the reasons given against rejection under 35 U.S.C. 103(a) is applicable for the above rejection also. Examiner respectfully disagrees. Examiner has rewritten the above rejection to make it more clearer and continues to maintain the above rejection.


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***Conclusion***

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

  
MANJUNATH RAO  
PATENT EXAMINER

Manjunath N. Rao, Ph.D.  
June 25, 2003